PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/436, A61P 27/02 — A1

(11) International Publication Number: **WO 00/66122**

(43) International Publication Date: 9 November 2000 (09.11.00)

(21) International Application Number: PCT/JP00/02756

(22) International Filing Date: 26 April 2000 (26.04.00)

(30) Priority Data:
60/132,009 30 April 1999 (30.04.99) US

(71) Applicant *(for all designated States except US)*: R-TECH UENO, LTD. [JP/JP]; 2-4-8, Koraibashi, Chuo-ku, Osaka-shi, Osaka 541-8543 (JP).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: UENO, Ryuji [JP/US]; 11025 Stanmore Drive, Potomac, Montgomery, MD 20854 (US).

(74) Agent: TAKASHIMA, Hajime; Yuki Building, 3-9, Hiranomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-0046 (JP).

(81) Designated States: AL, AU, BR, CA, CN, CZ, HU, IL, IN, JP, KR, LT, LV, MK, MX, NO, NZ, RO, RU, SI, TR, US, ZA, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: USE OF MACROLIDE COMPOUNDS FOR THE TREATMENT OF DRY EYE

(57) Abstract

The present invention provides an agent for treating a dry eye, which contains a macrolide compound such as FK506.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

SPECIFICATION

USE OF MACROLIDE COMPOUNDS FOR THE TREATMENT OF DRY EYE

Technical Field

The present invention relates to an agent for treating a dry eye.

Background Art

One of the symptoms of ophthalmic diseases drawing much attention these days is dry eye. The dry eye is defined to mean a condition wherein lacrimal fluid is less in amount or abnormal in quality, with or without the presence of corneal and conjunctival lesion (Yamada, M. et al., Folia Ophthalmol. Jpn., 43, 1289-1293 (1992)). Specific symptoms include dry eye observed in hypolacrimation, alacrima, xerophthalmia, Sjögren syndrome, keratoconjunctivitis sicca, Stevens-Johnson syndrome, ocular pemphigoid, marginal blepharitis, diabetes and the like, dry eye observed after cataract operation, dry eye in conjunction with allergic conjunctivitis and the like, and dry eye due to hypolacrimation caused by increased VDT (visual display terminal) work, dry room with air conditioning and the like.

The dry eye is caused by various factors that may not be entirely clear, and, at the moment, a drastic treatment method, such as promotion of the secretion of lacrimal fluid, has not been established yet. Therefore, the dry eye has been diagnosed according to the subjective symptoms obtained by questioning and objective symptoms known from lacrimal fluid evaluation tests (tear film breakup time, Schirmer test, lacrimal fluid clearance test and the like), corneal and conjunctival staining tests (fluorescein staining, rose bengale staining and the like), and the like. For example, tear film breakup time (BUT), which is one of the lacrimal fluid evaluation tests, reflects the stability of precorneal tear film, and means the time (sec) from complete nictitation to the initial breakage of the precorneal tear film. A lower BUT means severer dry eye symptom. In the case of severe dry eye, the breakage of the tear film occurs immediately after nictitation, which is rated as BUT zero (0) sec.

At present, a dry eye therapy includes increasing lacrimal fluid reservoir in conjunctival sac by instillation of artificial tears to alleviate the subjective symptoms of patients or to protect the eye from drying, and other methods.

For the above-mentioned therapy, instillation of chondroitin

sulfate, methyl cellulose and the like, and internal use of bromhexine hydrochloride, salivary gland hormone and the like have been the typical methods. However, the effect of such therapy is not necessarily satisfactory. While instillation of artificial tears and use of a goggle eye patch and the like have been the means to protect the eyes from drying, these are not more than auxiliary therapy methods.

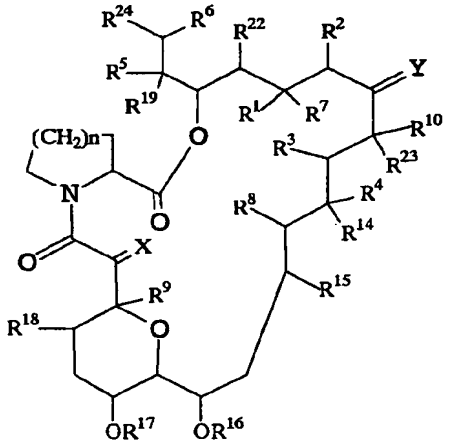
DISCLOSURE OF THE INVENTION

As a result of the intensive studies done by the present inventor, it was surprisingly found that a macrolide compound has a superior improving effect on dry eye symptoms, particularly subjective symptoms, and in lacrimal fluid evaluation tests, such as tear film breakup time and the like, and exhibits a superior therapeutic effect on the dry eye, which resulted in the completion of the present invention.

Accordingly, the present invention provides the following.

(1) An agent for treating a dry eye, comprising a macrolide compound as an active ingredient.

(2) The agent of (1), wherein the macrolide compound is a tricyclo compound (I) of the following formula



(I)

wherein adjacent pairs of R^1 and R^2, R^3 and R^4, and R^5 and R^6 each independently

a) consist of two adjacent hydrogen atoms, wherein R^2 is optionally alkyl, or

b) form another bond between carbon atoms binding with the members of each pair;

R^7 is hydrogen atom, hydroxy, alkyloxy or protected hydroxy, or may

form oxo with R^1 ;

R^8 and R^9 each independently show hydrogen atom or hydroxy ;

R^{10} is hydrogen atom, alkyl, alkenyl, alkyl substituted by one or more hydroxy, alkenyl substituted by one or more hydroxy, or alkyl substituted by oxo ;

X is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $-CH_2O-$;

Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R^{11} and R^{12} each independently show hydrogen atom, alkyl, aryl or tosyl ;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} each independently show hydrogen atom or alkyl ;

R^{24} is an optionally substituted ring that may contain one or more hetero atom(s) ; and

n is 1 or 2.

In addition to the meaning noted above, Y, R^{10} and R^{23} may form, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, wherein the heterocyclic group may be substituted by one or more group(s) selected from the group consisting of alkyl, hydroxy, alkyloxy, benzyl, a group of the formula $-CH_2Se(C_6H_5)$, and alkyl substituted by one or more hydroxy,

or a pharmaceutically acceptable salt thereof.

(3) The agent of (1) or (2), wherein the macrolide compound is FK506.

(4) The agent of any of (1) to (3), which is in the form of a preparation for local administration to the eye.

(5) The agent of any of (1) to (4), which aims at improving the tear film breakup time.

(6) A method for treating dry eye, comprising administering an effective amount of a macrolide compound to a subject in need of the treatment of dry eye.

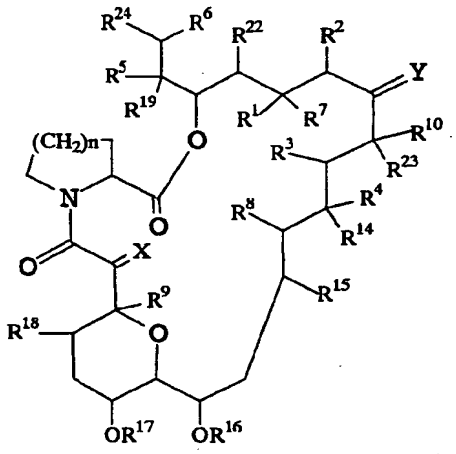
(7) Use of a macrolide compound for the production of a pharmaceutical composition for the treatment of dry eye.

DETAILED DESCRIPTION OF THE INVENTION

Some of the macrolide compounds to be used in the present invention are known as shown below and a novel macrolide compound can be prepared from these known macrolide compounds by a known method. Preferable examples thereof include macrolide compounds such as FK506, Ascomycin

derivative, Rapamycin derivative and the like.

Specific examples of macrolide compound include tricyclo compound (I) of the following formula and a pharmaceutically acceptable salt thereof.



(I)

wherein adjacent pairs of R^1 and R^2, R^3 and R^4, and R^5 and R^6 each independently

a) consist of two adjacent hydrogen atoms, wherein R^2 is optionally alkyl, or

b) form another bond between carbon atoms binding with the members of each pair;

R^7 is hydrogen atom, hydroxy, alkyloxy or protected hydroxy, or may form oxo with R^1;

R^8 and R^9 each independently show hydrogen atom or hydroxy;

R^{10} is hydrogen atom, alkyl, alkenyl, alkyl substituted by one or more hydroxy, alkenyl substituted by one or more hydroxy, or alkyl substituted by oxo;

X is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $-CH_2O-$;

Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R^{11} and R^{12} each independently show hydrogen atom, alkyl, aryl or tosyl;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} each independently show hydrogen atom or alkyl;

R^{24} is an optionally substituted ring that may contain one or more hetero atom(s); and

n is 1 or 2.

In addition to the meaning noted above, Y, R^{10} and R^{23} may form, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, wherein the heterocyclic group may be substituted by one or more group(s) selected from the group consisting of alkyl, hydroxy, alkyloxy, benzyl, a group of the formula $-CH_2Se(C_6H_5)$, and alkyl substituted by one or more hydroxy.

Preferable R^{24} is, for example, cyclo(C_5-C_7)alkyl optionally having suitable substituent, such as the following.

(a) 3,4-dioxocyclohexyl,

(b) 3-R^{20}-4-R^{21}-cyclohexyl,

wherein R^{20} is hydroxy, alkyloxy or $-OCH_2OCH_2CH_2OCH_3$, and R^{21} is hydroxy, -OCN, alkyloxy, heteroaryloxy optionally having suitable substituent, $-OCH_2OCH_2CH_2OCH_3$, protected hydroxy, chloro, bromo, iodo, aminooxalyloxy, azide, p-tolyloxythiocarbonyloxy, or $R^{25}R^{26}CHCOO-$ (wherein R^{25} is hydroxy optionally protected where desired or protected amino, and R^{26} is hydrogen atom or methyl),

or R^{20} and R^{21} in combination form an oxygen atom of epoxide ring, and

(c) cyclopentyl substituted by methoxymethyl, protected hydroxymethyl where desired, acyloxymethyl (wherein acyl moiety is optionally quaternized dimethylamino where desired or optionally esterified carboxy), one or more optionally protected amino and/or hydroxy, or aminooxalyloxymethyl. Preferable example includes 2-formyl-cyclopentyl.

The definition of each symbol used in the formula (I), specific examples thereof and preferable embodiments thereof are explained in detail in the following.

"Lower" means that a group has 1 to 6 carbon atoms unless otherwise indicated.

Preferable examples of "alkyl" and the alkyl moiety of "alkyloxy" include linear or branched aliphatic hydrocarbon residue, such as lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, neopentyl, hexyl and the like).

Preferable examples of "alkenyl" include linear or branched aliphatic hydrocarbon residue having one double bond, such as lower alkenyl (e.g., vinyl, propenyl (e.g., allyl and the like), butenyl, methylpropenyl, pentenyl, hexenyl and the like).

Preferable examples of "aryl" include phenyl, tolyl, xylyl,

cumenyl, mesityl, naphthyl and the like.

Preferable examples of the protective group of "protected hydroxy" and "protected amino" include 1-(lower alkylthio)(lower)alkyl such as lower alkylthiomethyl (e.g., methylthiomethyl, ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, butylthiomethyl, isobutylthiomethyl, hexylthiomethyl and the like), with more preference given to C_1 - C_4 alkylthiomethyl and most preference given to methylthiomethyl;

tri-substituted silyl such as tri(lower)alkylsilyl (e.g., trimethylsilyl, triethylsilyl, tributylsilyl, tert-butyldimethylsilyl, tri-tert-butylsilyl and the like), and lower alkyldiarylsilyl (e.g., methyldiphenylsilyl, ethyldiphenylsilyl, propyldiphenylsilyl, tert-butyldiphenylsilyl and the like, with more preference given to tri(C_1-C_4)alkylsilyl and C_1-C_4 alkyldiphenylsilyl, and most preference given to tert-butyldimethylsilyl, tert-butyldiphenylsilyl;

acyl such as aliphatic acyl derived from carboxylic acid, sulfonic acid and carbamic acid, aromatic acyl, and aliphatic acyl substituted by aromatic group; and the like.

The aliphatic acyl is exemplified by lower alkanoyl optionally having one or more suitable substituent(s) (e.g., carboxy) such as formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, carboxyacetyl, carboxypropionyl, carboxybutyryl, carboxyhexanoyl and the like;

cyclo(lower)alkyloxy(lower)alkanoyl optionally having one or more suitable substituent(s) (e.g., lower alkyl) such as cyclopropyloxyacetyl, cyclobutyloxypropionyl, cycloheptyloxybutyryl, mentyloxyacetyl, mentyloxypropionyl, mentyloxybutyryl, mentyloxypentanoyl, mentyloxyhexanoyl and the like, camphorsulfonyl;

lower alkylcarbamoyl having one or more suitable substituent(s) such as carboxy or protected carboxy and the like, such as carboxy(lower)alkylcarbamoyl (e.g., carboxymethylcarbamoyl, carboxyethylcarbamoyl, carboxypropylcarbamoyl, carboxybutylcarbamoyl, carboxypentylcarbamoyl, carboxyhexylcarbamoyl) and

tri(lower)alkylsilyl(lower)alkyloxycarbonyl(lower)-alkylcarbamoyl (e.g., trimethylsilylmethoxycarbonylethylcarbamoyl, trimethylsilylethoxycarbonylpropylcarbamoyl,

triethylsilylethoxycarbonylpropylcarbamoyl, tert-butyldimethylsilylethoxycarbonylpropylcarbamoyl, trimethylsilylpropoxycarbonylbutylcarbamoyl); and the like.

Aromatic acyl is exemplified by aroyl optionally having suitable substituent(s) (e.g., nitro), such as benzoyl, toluoyl, xyloyl, naphthoyl, nitrobenzoyl, dinitrobenzoyl, nitronaphthoyl and the like ; and arenesulfonyl optionally having one or more suitable substituent(s) (e.g., halogen), such as benzenesulfonyl, toluenesulfonyl, xylenesulfonyl, naphthalenesulfonyl, fluorobenzenesulfonyl, chlorobenzenesulfonyl, bromobenzenesulfonyl, iodobenzenesulfonyl and the like.

The aliphatic acyl substituted by aromatic group may be, for example, ar(lower)alkanoyl optionally having one or more suitable substituent(s) (e.g., lower alkyloxy or trihalo(lower)alkyl and the like), wherein specific examples are phenylacetyl, phenylpropionyl, phenylbutyryl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl, 2-ethyl-2-trifluoromethyl-2-phenylacetyl, 2-trifluoromethyl-2-propoxy-2-phenylacetyl and the like.

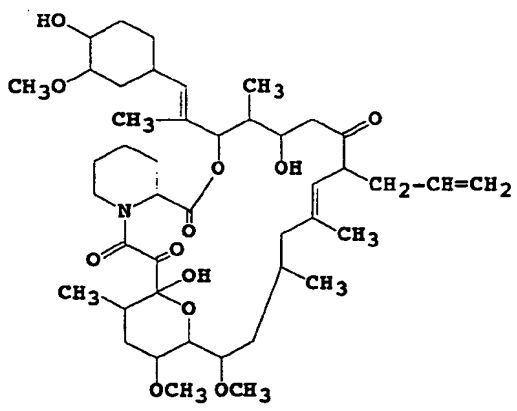
Of the above-mentiond acyl, more preferable acyl includes C_1 - C_4 alkanoyl optionally having carboxy, cyclo(C_5 - C_6)alkyloxy(C_1 - C_4)alkanoyl having two (C_1 - C_4)alkyl in the cycloalkyl moiety, camphorsulfonyl, carboxy (C_1 - C_4)alkylcarbamoyl, tri(C_1 - C_4)alkylsilyl(C_1 - C_4)alkyloxycarbonyl(C_1 - C_4)alkylcarbamoyl, benzoyl optionally having 1 or 2 nitro groups, benzenesulfonyl having halogen, and phenyl(C_1 - C_4)alkanoyl having C_1 - C_4 alkyloxy and trihalo(C_1 - C_4)alkyl. Of these, most preferred are acetyl, carboxypropionyl, mentyloxyacetyl, camphorsulfonyl, benzoyl, nitrobenzoyl, dinitrobenzoyl, iodobenzenesulfonyl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl and the like.

Preferable examples of the "heterocyclic group consisting of saturated or unsaturated 5 or 6-membered ring having nitrogen atom, sulfur atom and/or oxygen atom" are pyrolyl, tetrahydrofuryl and the like.

The "heteroaryl optionally having a suitable substituent" moiety of the "heteroaryloxy optionally having a suitable substituent" is that exemplified for R^1 of the compound of the formula I of EP-A-532,088, with preference given to 1-hydroxyethylindol-5-yl. This publication is incorporated hereinto by reference.

The tricyclo compound (I) and a pharmaceutically acceptable salt thereof to be used in the present invention have immunosuppressive action, antibacterial action and other pharmacological activity, so that they are useful for the prophylaxis and treatment of rejection in organ or tissue transplantation, graft versus host reaction, autoimmune diseases, infectious diseases and the like, as noted, together with the production method thereof, in, for example, EP-A-184162, EP-A-323042, EP-A-423714, EP-A-427680, EP-A-465426, EP-A-480623, EP-A-532088, EP-A-532089, EP-A-569337, EP-A-626385, WO89/05303, WO93/05058, WO96/31514, WO91/13889, WO91/19495, WO93/5059 and the like, all of these publications are hereby incorporated by reference.

In particular, the compounds called FR900506 (=FK506), FR900520 (Ascomycin), FR900523 and FR900525 are produced by the genus *Streptomyces*, such as *Streptomyces tsukubaensis*, No. 9993 (depository : National Institute of Bioscience and Human-Technology Agency of Industrial Science and Technology, the Ministry of International Trade and Industry, 1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken, Japan (formerly : Fermentation Research Institute, Agency of Industrial Science and Technology, the Ministry of International Trade and Industry), date of deposit : October 5, 1984, deposit number : FERM BP-927) or *Streptomyces hygroscopicus subsp. Yakushimaensis*, No. 7238 (depository : National Institute of Bioscience and Human-Technology Agency of Industrial Science and Technology, 1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken, Japan (formerly : Fermentation Research Institute, Agency of Industrial Science and Technology, the Ministry of International Trade and Industry), date of deposit : January 12, 1985, deposit number : FERM BP-928 (EP-A-0184162)). The compound of the following formula, FK506 (general name : Tacrolimus), is a representative compound.



Chemical name : 17-allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

Of the tricyclo compounds (I), more preferred is a compound wherein adjacent pairs of R^3 and R^4, and R^5 and R^6 each independently form another bond between carbon atoms binding with the members of each pair ;

R^8 and R^{23} each independently show hydrogen atom ;

R^9 is hydroxy ;

R^{10} is methyl, ethyl, propyl or allyl ;

X is (hydrogen atom, hydrogen atom) or oxo ;

Y is oxo ;

R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19} and R^{22} each independently show methyl ;

R^{24} is 3-R^{20}-4-R^{21}-cyclohexyl,

wherein R^{20} is hydroxy, alkyloxy or $-OCH_2OCH_2CH_2OCH_3$, and

R^{21} is hydroxy, -OCN, alkyloxy, heteroaryloxy optionally having suitable substituent, $-OCH_2OCH_2CH_2OCH_3$, protected hydroxy, chloro, bromo, iodo, aminooxalyloxy, azide, p-tolyloxythiocarbonyloxy or $R^{25}R^{26}CHCOO-$ (wherein R^{25} is hydroxy optionally protected where desired, or protected amino, and R^{26} is hydrogen atom or methyl), or R^{20} and R^{21} in combination form an oxygen atom of epoxide ring; and

n is 1 or 2.

Particularly preferable tricyclo compound (I) includes, besides FK506, Ascomycin derivatives such as halogenated derivative of 33-epi-chloro-33-desoxy Ascomycin described in Example 66a of

EP-A-427,680 and the like.

Other preferable macrolide compounds include Rapamycin described in MERCK INDEX, 12 edition, No. 8288 and derivatives thereof. Preferable examples thereof include O-substituted derivative described at page 1 of WO95/16691, formula A, wherein the 40th hydroxy is -OR_1 (wherein R_1 is hydroxyalkyl, hydroalkyloxyalkyl, acylaminoalkyl or aminoalkyl), such as 40-O-(2-hydroxy)ethyl Rapamycin, 40-O-(3-hydroxy)propyl Rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl Rapamycin and 40-O-(2-acetaminoethyl) Rapamycin. These O-substituted derivatives can be produced by reacting, under appropriate conditions, Rapamycin (or dihydro or deoxo Rapamycin) and an organic radical bound with a leaving group (e.g., RX wherein R is an organic radical desirable as O-substituent, such as alkyl, allyl and benzyl moiety, and X is a leaving group such as $CCl_3C(NH)O$ and CF_3SO_3)). The conditions are: when X is $CCl_3C(NH)O$, acidic or neutral conditions, such as in the presence of trifluoromethanesulfonic acid, camphorsulfonic acid, p-toluenesulfonic acid or their corresponding pyridinium or substituted pyridinium salt, and when X is CF_3SO_3, in the presence of a base such as pyridine, substituted pyridine, diisopropylethylamine and pentamethylpiperidine. The most preferable Rapamycin derivative is 40-O-(2-hydroxy)ethyl Rapamycin as disclosed in WO94/09010. The contents of the above references are hereby incorporated into the specification by reference.

The pharmaceutically acceptable salt of tricyclo compound (I), Rapamycin and derivatives thereof are nontoxic and pharmaceutically acceptable conventional salts, which are exemplified by salts with inorganic or organic base such as alkali metal salt (e.g., sodium salt, potassium salt and the like), alkaline earth metal salt (e.g., calcium salt, magnesium salt and the like), ammonium salt, and amine salt (e.g., triethylamine salt, N-benzyl-N-methylamine salt and the like).

In the macrolide compound of the present invention, conformer or one or more pairs of stereoisomers, such as optical isomers and geometric isomers, may be included due to asymmetric carbon atom and double bond. Such conformers and isomers are also encompassed in the present invention. In addition, macrolide compounds can form solvates, which case is also encompassed in the present invention. Preferable solvate is exemplified by hydrates and ethanolates.

The diseases associated with dry eye in the present invention

include those mentioned above inclusive of hypolacrimation, alacrima xerophthalmia, Sjögren syndrome, keratoconjunctivitis sicca, Stevens-Johnson syndrome, ocular pemphigoid, marginal blepharitis, diabetes and the like, dry eye observed after cataract operation, that in conjunction with allergic conjunctivitis and the like. The dry eye similar to hypolacrimatioin is also observed, which is caused by VDT work and dry room due to air conditioning and the like.

The treatment agent of the present invention is effective against the above-mentioned dry eye and for the improvement of subjective symptoms, particularly dry eye, and in evaluation of tears, such as tear film breakup time (BUT) and the like.

The treatment in the context of the present invention includes any management such as prevention, cure, alleviation of symptom, reduction of symptom, prevention of progression and the like.

The macrolide compound to be used in the present invention can be used as a pharmaceutical agent for human and animals, and can be administered systemically or locally by oral administration, intravenous administration (inclusive of transfusion), subcutaneous administration, rectal or virginal administration, administration to local site in the eye (inclusive of eye ointment). In consideration of systemic influence, significant expression of the effect and the like, it is particularly preferably used in the form for local administration to the eye.

The dose of the macrolide compound varies depending on the kind, age, body weight of the administration subject such as human and animal, conditions to be treated, desired therapeutic effect, administration method, treatment period and the like. Generally, when it is administered systemically, the dose is about 0.0001 - 1000 mg, preferably 0.001 - 500 mg, which is given in a single dose or 2 to 4 dividual doses a day or administered in a sustained manner. When it is administered locally to the eye, a preparation containing the active ingredient in a proportion of 0.001 - 10.0 w/v%, preferably 0.005 - 5.0 w/v%, is applied to one eye several times a day, preferably instilled or applied 1 to 6 times a day.

According to the present invention, a macrolide compound, which is an active ingredient, can be administered alone or in combination with other pharmacologically active components. When administered after formulating a preparation, it can be administered as a preparation

produced by a conventional method. The dosage form may be, for example, eye drop, eye ointment, powder, granule, tablet, capsule, injection, ointment and the like, with particular preference given to eye drop and eye ointment. Such preparation can be produced according to a conventional method. Of such preparations, an oral preparation is preferably a solid solution preparation produced in the same manner as in the preparation of EP-A-0240773. When an eye drop is desired, an eye drop as described in EP-A-0406791 is preferable. When desired, additives generally used for eye drop, such as isotonizing agent (e.g., sodium chloride), buffering agent (e.g., boric acid, disodium hydrogenphosphate, sodium dihydrogenphosphate and the like), preservative (e.g., benzalkonium chloride, benzetonium chloride, chlorobutanol and the like), tackifier [e.g., sugar (lactose, mannitol, maltose and the like), hyaluronic acid or salt thereof (sodium hyaluronate, potassium hyaluronate and the like), mucopolysaccharide (e.g., chondroitin sulfate and the like), sodium polyacrylate, carboxy vinyl polymer, crosslinked polyacrylate, and the like] may be added. The contents of the above references in this respect are hereby incorporated into the specification by reference.

The present invention is explained in more detail in the following by referring to Examples. The present invention is not limited to these examples.

Examples

Example 1

Using FK506 as the active ingredient in the present invention, a 0.06% eye drop (suspension) having the following formulation was used as a test drug.

Test drug

A suspension having the following formulation was produced in the same manner as in EP-A-0406791 (Example 6).

FK506	0.6 mg
polyvinyl alcohol	7.0 mg
disodium hydrogenphosphate 12 hydrate	0.05 mg
sodium dihydrogenphosphate 2 hydrate	0.76 mg
phosphoric acid	appropriate amount
sodium hydroxide	appropriate amount
sodium chloride	8.56 mg
benzalkonium chloride	0.1 mg
injectable water	appropriate amount
Total amount	1 ml

The above-mentioned test drug was consecutively administered twice a day for two weeks to a male (44 years old) having subjective symptoms of dry eye (sense of dryness, foreign body and grittiness) and, as a result, the subjective symptoms disappeared.

From the above result, the test drug was confirmed to be effective for the improvement of subjective symptoms of dry eye.

Example 2

A suspension having the same formulation as in Example 1 was produced using FK506 as the active ingredient to give a 0.01% FK506 eye drop (suspension) and 0.1% FK506 eye drop (suspension) as test drugs. The base for the eye drops was used as the control drug.

The above-mentioned test drugs and the control drug were instilled four times a day for 7 days to 18 healthy subjects (6 per group) at 8:00, 11:00, 14:00 and 17:00.

The tear film breakup time (sec) of the right eye was measured before instillation and 8 days after instillation. The difference between before and after the instillation was calculated, and taken as the mean variation of the tear film breakup time.

The tear film breakup time was measured according to the conventional method. After instillation of fluorescein, the tear film was formed on the surface of the eye by nictitation. The surface of the eye was observed with a microscope without allowing nictitation, and the time until breakage of the tear film (burst by surface tension) was measured. The results are shown in Table 1.

Table 1

Group	Mean variation of tear film breakup time (sec)
Control drug group	+0.17
0.01% FK506 eye drop group	+0.58
0.1% FK506 eye drop group	+0.75

From the above results, the test drug was confirmed to be effective for the improvement of the tear film breakup time, which is one of the tests for lacrimal fluid evaluation of dry eye.

Industrial applicability

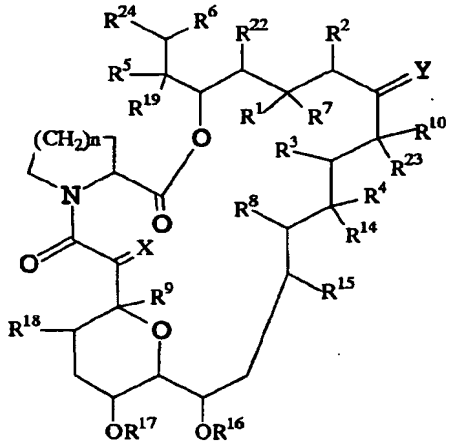
The treatment agent of the present invention, which comprises a macrolide compound as an active ingredient, has a superior improving effect on dry eye, particularly subjective symptom of dry eye and in lacrimal fluid evaluation such as tear film breakup time and the like. Therefore, the treatment agent of the present invention is suggested to be useful as an agent for treating dry eye.

This application is based on application No. 60/132,009 filed in United States of America, the content of which is incorporated hereinto by reference.

CLAIMS

1. An agent for treating a dry eye, comprising a macrolide compound as an active ingredient.

2. The agent of claim 1, wherein the macrolide compound is a tricyclo compound (I) of the following formula



(I)

wherein

adjacent pairs of R^1 and R^2, R^3 and R^4, and R^5 and R^6 each independently

a) consist of two adjacent hydrogen atoms, wherein R^2 is optionally alkyl, or

b) form another bond between carbon atoms binding with the members of each pair;

R^7 is hydrogen atom, hydroxy, alkyloxy or protected hydroxy, or may form oxo with R^1;

R^8 and R^9 each independently show hydrogen atom or hydroxy;

R^{10} is hydrogen atom, alkyl, alkenyl, alkyl substituted by one or more hydroxy, alkenyl substituted by one or more hydroxy, or alkyl substituted by oxo;

X is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $-CH_2O-$;

Y is oxo, (hydrogen atom, hydroxy), (hydrogen atom, hydrogen atom), or a group of the formula $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R^{11} and R^{12} each independently show hydrogen atom, alkyl, aryl or tosyl;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} each independently show hydrogen

atom or alkyl ;

R^{24} is an optionally substituted ring which optionally contains one or more hetero atom(s) ; and

n is 1 or 2,

wherein

Y, R^{10} and R^{23} optionally form, together with the carbon atom they bind with, a saturated or unsaturated 5 or 6-membered heterocyclic group containing nitrogen atom, sulfur atom and/or oxygen atom, the heterocyclic group may be substituted by one or more group(s) selected from the group consisting of alkyl, hydroxy, alkyloxy, benzyl, a group of the formula $-CH_2Se(C_6H_5)$, and alkyl substituted by one or more hydroxy,

or a pharmaceutically acceptable salt thereof.

3. The agent of claim 1 or claim 2, wherein the macrolide compound is FK506.

4. The agent of any of claim 1 to claim 3, which is in the form of a preparation for local administration to the eye.

5. The agent of any of claim 1 to claim 4, which aims at improving tear film breakup time.

6. A method for treating a dry eye, comprising administering an effective amount of a macrolide compound to a subject in need of the treatment of dry eye.

7. Use of a macrolide compound for the production of a pharmaceutical composition for the treatment of dry eye.

INTERNATIONAL SEARCH REPORT

Intern· ·al Application No
PCT/JP 00/02756

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/436 A61P27/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YANG, JIHONG ET AL: "Sjogren's syndrome in mice carrying the lprcg gene and the therapeutic efficacy of an immunosuppressive agent FK506" PATHOL. INT. (1999), 49(2), 133-140 , - February 1999 (1999-02) XP000952466 the whole document ---	1-4,6,7
P,X	DATABASE WPI Derwent Publications Ltd., London, GB; AN 2000-038597 XP002150034 YAMANAKA MASAYUKI: "Compositions containing macrolide compounds have high stability and adsorbability." & WO 99 55332 A (FUJISAWA PHARMA CO LTD), 16 November 1999 (1999-11-16) abstract --- -/--	1-4,6,7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 October 2000	24/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Veronese, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern ıal Application No
PCT/JP 00/02756

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	TSUBOTA K: "New approaches to dry-eye therapy" INTERNATIONAL OPHTHALMOLOGY CLINICS,US,LITTLE, BROWN, BOSTON, vol. 34, no. 1, 1994, pages 115-128, XP002120709 ISSN: 0020-8167 * See page 124: paragraph "Cyclosprin A" *	1-4,6,7
X	IWAMOTO H ET AL: "Inhibitory effects of FK506 on the development of experimental allergic/immune-mediated blepharoconjunctivitis in Lewis rats by systemic but not by topical administration." GRAEFES ARCHIVE FOR CLINICAL AND EXPERIMENTAL OPHTHALMOLOGY, (1999 MAY) 237 (5) 407-14. , XP000952455 the whole document	1-4,6,7
X	WO 97 25977 A (CIBA GEIGY AG ;TIEMESSEN HARRY (DE)) 24 July 1997 (1997-07-24) page 14, line 8	1-4,6,7
X	WO 96 31514 A (SANDOZ LTD ;SANDOZ AG (DE); SANDOZ AG (AT); HERSPERGER RENE (CH);) 10 October 1996 (1996-10-10) page 16, last line	1,2,4-7
P,X	WO 00 09109 A (GUILFORD PHARM INC) 24 February 2000 (2000-02-24) claims; example 11	1,4,6,7
A	TSUJIKAWA A ET AL: "TACROLIMUS (FK506) ATTENUATES LEUKOCYTE ACCUMULATION AFTER TRANSIENT RETINAL ISCHEMIA" STROKE,US,AMERICAN HEART ASSOCIATION, DALLAS TX, vol. 29, no. 7, 1998, pages 1431-1438, XP000913599 ISSN: 0039-2499 the whole document	1-7
A	EP 0 532 862 A (UNIV LOUISVILLE RES FOUND) 24 March 1993 (1993-03-24) claims; examples	1-7

-/--

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern ıal Application No
PCT/JP 00/02756

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	TABBARA K F ET AL: "DRY EYE SYNDROME" DRUGS OF TODAY / MEDICAMENTOS DE ACTUALIDAD,ES,J.R. PROUS SS.A. INTERNATIONAL PUBLISHERS, vol. 34, no. 5, 1998, pages 447-453, XP000872457 ISSN: 0025-7656 the whole document	1-7

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

...ormation on patent family members

Intern :al Application No
PCT/JP 00/02756

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9955332 A	04-11-1999	AU 3537299 A	16-11-1999
WO 9725977 A	24-07-1997	AU 1543497 A	11-08-1997
		CA 2240339 A	24-07-1997
		EP 0874621 A	04-11-1998
		JP 2000503655 T	28-03-2000
WO 9631514 A	10-10-1996	AU 703523 B	25-03-1999
		AU 5645396 A	23-10-1996
		BR 9604808 A	09-06-1998
		CA 2216562 A	10-10-1996
		CZ 9703123 A	14-01-1998
		EP 0819130 A	21-01-1998
		FI 973529 A	25-11-1997
		HU 9801993 A	28-12-1998
		JP 2000505044 T	25-04-2000
		NO 974536 A	01-10-1997
		NZ 307170 A	29-03-1999
		PL 322553 A	02-02-1998
		SK 133997 A	06-05-1998
		US 5925649 A	20-07-1999
WO 0009109 A	24-02-2000	AU 5555799 A	06-03-2000
EP 0532862 A	24-03-1993	AT 133336 T	15-02-1996
		AU 653415 B	29-09-1994
		AU 2035092 A	28-01-1993
		CA 2074641 A	26-01-1993
		CZ 285660 B	13-10-1999
		DE 69207847 D	07-03-1996
		DE 69207847 T	30-05-1996
		DK 532862 T	19-02-1996
		ES 2083030 T	01-04-1996
		HK 1005705 A	22-01-1999
		HU 211218 B	28-11-1995
		IL 102414 A	04-08-1996
		JP 2568962 B	08-01-1997
		JP 5194212 A	03-08-1993
		KR 216768 B	01-09-1999
		MX 9204381 A	01-02-1993
		NZ 243679 A	24-06-1997
		SK 230792 A	08-05-1996
		RU 2048812 C	27-11-1995
		US 5387589 A	07-02-1995
		ZA 9204953 A	28-04-1993